correlating the levels of the [apolipoproteins] apolipoprotein subtypes in the serum based on the levels of [apolipoproteins] apolipoprotein subtypes determined in the saliva sample, and

extrapolating the levels of [HDL and/or LDL] the lipoprotein in the serum, based on the levels of the [apolipoproteins] apolipoprotein subtypes determined in the saliva sample.

22. (amended) The method of claim 20 comprising reacting the apolipoprotein in the saliva sample with antibodies specifically immunoreactive with an apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, and Apo E, [and components thereof,] and

correlating the levels of at least one apolipoprotein in the saliva with the levels of apolipoprotein in serum samples of patients having [known to be correlated to the presence of] lipid disorders or risk of cardiovascular disease.

Remarks

Rejections Under 35 U.S.C. § 103

Claims 1-3, 5-7, 10-14, 16-18, and 20-22 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,677,133 to Oberhardt ("Oberhardt '133") or U.S. Patent No. 5,601,991 to Oberhardt ("Oberhardt '991"), in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and U.S. Patent No. 6,291,178 to Schneider ("Schneider"). Claims 1 and 4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,210,906 to Kundu et al. ("Kundu"), in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and U.S. Patent No. 6,291,178 to Schneider ("Schneider"). Claims 8-9, 15 and 19 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,677,133 to Oberhardt ("Oberhardt '133") or U.S. Patent No. 5,601,991 to Oberhardt ("Oberhardt '991"), in view of

U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman"), and U.S. Patent No. 6,291,178 to Schneider ("Schneider"), and in further view of Fisher et al. (Diabetes Research and Clinical Practice, 1991) ("Fisher") and Coppo et al. (Journal of Diabetic Complications, 1987) ("Coppo"). These rejections are respectfully traversed.

Claim 1 is drawn to a method for determining the level of an apolipoprotein in saliva comprising

(1) reacting the apolipoproteins in a saliva sample with antibodies immunoreactive with the apolipoprotein,

(2) quantitating the amounts of apolipoproteins in the saliva sample, and

(3) comparing the amounts of apolipoproteins in the saliva sample with standards of the corresponding amounts of apolipoproteins in serum samples to determine the level of apolipoproteins in the serum of the individual from whom the saliva was collected.

The Prior Art

The prior art does not disclose each claimed element. In particular, the prior art fails to disclose at least one critical element - that saliva apolipoprotein levels can be correlated with serum apolipoprotein levels.

The examiner has recognized that neither Oberhardt nor Fellman disclose this element and has relied on Schneider as disclosing this element (see page 10 of the office action). However, Schneider is not available as prior art to this application.

U.S. patent No. 6,291,178 to Schneider issued on an application filed August 30, 1999. The present application claims priority to U.S.S.N. 60/124,562 filed March 16, 1999. Although Schneider claims priority to U.S.S.N. 08/978,729 filed November 26, 1997, a review of U.S. Patent No. 5,968,746 which issued on U.S.S.N. 08/978,729 fails to identify even a single occurrence of the word "apolipoprotein" or "cholesterol". The '746 patent is drawn entirely to the use of a saliva sample for measurement of drugs (see col. 1, col. 2, lines 42-45, claim 6). Therefore the '562 Schneider patent is not available as prior art to this application. All the priority application discloses is that one can measure the presence of drugs in saliva. There is not even an indication that it is, or would be expected to be, correlated with the actual blood levels.

Oberhardt '133 and Oberhardt '991

Oberhardt '991 teaches a method and a system of dry chemistry cascade immunoassay and affinity assay. Both Oberhardt patents do not teach the detection of levels of apolipoprotein in saliva or a correlation between apolipoprotein levels in saliva and blood. Oberhardt does not provide motivation to detect levels of apolipoprotein in saliva. Neither of these patents enables one of ordinary skill to detect the levels of lipoproteins in saliva and extrapolate to the serum concentrations. These patents provide no description of saliva collection, removal of mucopolysaccharides, or reason to remove mucopolysaccharides.

Fellman

Fellman discloses a means for reducing the viscosity of a body fluid sample such as saliva which contains mucopolysaccharides, using a cationic quaternary ammonium reagent. Fellman does not teach detecting apolipoproteins in saliva with antibodies, or that the levels can be correlated with levels in serum. Fellman does not teach a quantitative assay kit comprising collection mean, antibodies to apolipoprotein, and means to compare saliva and serum apolipoprotein levels.

Kundu

Kundu teaches specific antibodies to Apo A and methods to use the antibodies. Similar to the Oberhardt patents, Kundu does not teach why or how the levels of apolipoproteins should be detected in saliva, nor how to correlate the levels of the apolipoproteins in the saliva with the levels of the apolipoproteins in the serum, as defined by the claims. Kundu does not teach removal of mucopolysaccharides, or reason to remove mucopolysaccharides,

Fisher and Coppo

Fisher and Coppo provide assays for detecting albumin, one in saliva and one in urine. Neither suggest detecting apolipoprotein in saliva, nor that the levels could be correlated with the levels in the serum by measuring the values of the albumin.

Oberhardt in combination with Fellman, Fisher and Coppo

As discussed above, Oberhardt in combination with Fellman does not disclose the claimed methods or lit either alone or in combination. Fisher and Coppo do not make up for these deficiencies.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed.

Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit recently warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit teachings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

It has been made very clear that "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Further, the "level of skill in the art cannot be relied upon to provide the suggestion to

combine references. *Al-site Corp v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

In the present case, there is no teaching in the prior art that would suggest combining the references and then modifying them for a different purpose, as applicants have done. There is no motivation to combine these references to obtain all the claim limitations. Oberhardt does not recite a need to remove mucopolysaccharides from the sample and Fellman does not recite a need to use their method to detect apolipoprotein levels. One of skill in the art would not be motivated to combine these references absent the teachings of the present specification.

Kundu does not teach a means for collecting saliva nor a process to correlate the results of saliva and serum. Fellman does not recite a need to use their method to detect apolipoprotein levels. There is no motivation to combine these references and modify them as applicants have done. One of skill in the art would not be motivated to combine these references absent the teachings of the present specification. Fisher and Coppo do not make up for these deficiencies. One of skill in the art would not find the claimed methods or kit obvious absent the teachings of the present specification.

At the time of this application was filed, there was so much inherent variability in the saliva that although apolipoprotein was clearly present, the samples could not routinely be assayed and yield a reliable result. The examiner's attention is drawn to the prior art discussed at page 4 of the application in this regard. The examiner has provided no art that demonstrates that the prior art was not entirely inconsistent.

The Applicants have developed a method to measure the apolipoprotein levels in saliva and correlate them to levels in the serum in order to circumvent the issue of saliva variability. This application presents a novel, unobvious method and kit to quantitatively assay apolipoprotein levels in saliva.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-11 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended. Claims 1, 20 and 22 in particular have been amended in view of the extremely helpful suggestions by the examiner.

Claim 1 has been amended to define specific method steps:

A method for determining the level of an apolipoprotein in the serum of an individual based on levels of the apolipoprotein in the individual's saliva comprising

obtaining a saliva sample from an individual,

reacting the apolipoproteins in the saliva sample with antibodies immunoreactive with one or more of the apolipoproteins, wherein the antibodies are in a quantitative assay, and

etermining the amount of apolipoproteins in the serum of the individual by comparing the immunoreactivity between the antibodies and apolipoproteins in the saliva sample by reference to standards of known amounts of apolipoproteins in saliva and serum.

The claim now defines each step that would be undertaken by a nurse or lab technician at a clinic that would be practicing the claimed method. Specifically, an individual would come in

and collect a saliva sample that would be handed to the nurse or technician. Page 11 describes available technology for collection of saliva samples. The nurse or technician would take the saliva sample, add antibodies in a quantitative assay (such as those recited at pages 12-13) which would react with the apolipoproteins in the saliva sample, then they would compare the degree of immunoreactivity (typically measured using a colorimetric or chromatographic assay, as described at pages 13-15) with reference standards (pages 18-19; page 20, lines 9-11), that would indicate the level(s) of the apolipoproteins. Support for the amendments is also found in Table 3, which demonstrates actual reduction to practice and correlation between serum and saliva levels.

Claim 2, 14, 20 and 22 have been amended to delete the reference to the "components" of Apo A-E as being immunoreactive with apolipoprotein antibodies.

Claim 10 has been amended to clarify that the saliva is collected into a device for filtration of the mucopolysaccharide as well as determination of the levels of the apolipoprotein.

Claim 19 has been amended to clarify that the two antibodies in the assay device or kit of claim 15 exist as separate antibodies, not a combination of the two.

Claim 20 has been amended along the lines of claim 1. It is believed the comments in this section of the office action at page 5 were meant to refer to claim 20, not claim 1.

Claim 21 has been amended to define high density lipoproteins and low density lipoproteins and to replace the indefinite "and/or" phrase with a Markush group. The relationship between HDL/LDL and apolipoproteins is also defined. Support for this amendment is found on page 2, lines 4-11 of the specification.

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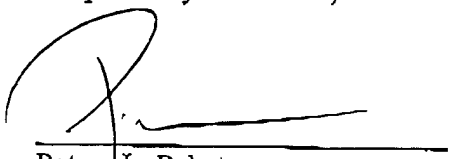
AMENDMENT

Claim 22 has been amended to clarify the correlation step between apolipoproteins in serum and saliva to correlate to the presence of lipid disorders or risk of cardiovascular disease, using language suggested by the examiner.

Allowance of claims 1-22 is respectfully solicited.

Respectfully submitted,



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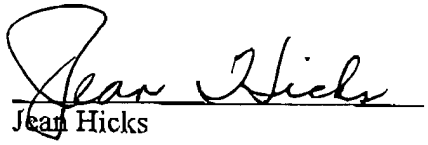
Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, February 12, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.



Jean Hicks

Date: February 25, 2003

U.S.S.N. 08/924,994
FILED: SEPTEMBER 5, 1998
MARKED UP VERSION OF CLAIMS AS AMENDED

Marked Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Three times amended) A method for determining the level of an apolipoprotein in [saliva] the serum of an individual based on levels of the apolipoprotein in the individual's saliva comprising

obtaining a saliva sample from an individual,

reacting the apolipoproteins in [a] the saliva sample with antibodies immunoreactive with [the apolipoprotein] one or more of the apolipoproteins, wherein the antibodies are in a quantitative assay which measures the amount or concentration of bound complexes between apolipoproteins and the antibodies immunoreactive therewith,

[using a quantitative assay kit comprising means for collection of saliva, and antibodies immunoreactive with an apolipoprotein and means for comparing the levels of the apolipoproteins in the saliva with the levels in serum,]

[detecting] determining the amount of apolipoproteins in the serum of the individual by comparing the immunoreactivity between the antibodies and apolipoproteins in the saliva sample [as determined by the quantitative assay] by reference to [, and

comparing the amount of determined immunoreactivity with] standards of known amounts of apolipoproteins in saliva and serum [reacted with the antibodies to determine the level of apolipoproteins in the saliva sample].

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MARKED UP VERSION OF CLAIMS AS AMENDED

2. (Amended) The method of claim 1 wherein the apolipoprotein is selected from the group consisting of Apo A, Apo B, Apo C, and Apo E[, and components thereof].

3. The method of claim 2 wherein the apolipoprotein is selected from the group consisting of Apo A1 and Apo B.

4. (Amended) The method of claim 1 wherein the antibodies are labelled with a detectable label.

5. (amended) The method of claim 1 further comprising determining the level of apolipoprotein in the saliva sample within less than three hours following collection.

6. (twice Amended) The method of claim 1 further comprising preparing the saliva in the sample by removing mucopolysaccharides from the saliva prior to determining the level of apolipoprotein in the saliva sample.

7. (amended) The method of claim 1 further comprising collecting the saliva after stimulating its secretion from a subject.

8. The method of claim 1 further comprising determining the amount of albumin present in the saliva.

9. (twice Amended) The method of claim 8 further comprising correcting the determined amount of the apoplipoprotein for the presence of albumin in the saliva sample.

10. (twice amended) The method of claim 1 [further comprising collecting] wherein the saliva sample is collected into a device which filters out mucopolysaccharides and which

comprises the antibodies immunoreactive with one or more of the apolipoproteins in the saliva sample.

11. The method of claim 10 wherein the apolipoprotein is either Apo A1 or Apo B.

12. (amended) An assay device or kit for determining the amount of apolipoprotein in a saliva sample comprising

means for collection of saliva, [and]

antibodies immunoreactive with [an apolipoprotein] <u>one or more apolipoproteins, wherein the antibodies are in a quantitative assay which measures the amount or concentration of bound complexes between apolipoproteins and the antibodies immunoreactive therewith</u> [for use in a quantitative assay], and

[means for comparing the levels of the apolipoproteins in the saliva with the levels in serum] <u>standards of known amounts of apolipoproteins in saliva and serum</u>.

13. (amended) The assay device or kit of claim 12 comprising filter means for removal of mucopolysaccharides from the saliva.

14. (amended) The assay device or kit of claim 12 wherein the antibodies are reactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, <u>and</u> Apo E[, and components thereof].

15. The assay device or kit of claim 12 further comprising antibodies immunoreactive with albumin.

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16. (twice Amended) The assay device or kit of claim 12 wherein the antibodies immunoreactive with apolipoprotein in the saliva sample are immobilized on a solid support.

17. The assay device or kit of claim 16 comprising reagents for detection of complexes between the apolipoprotein and the antibodies.

18. (Amended) The assay device or kit of claim 12 comprising a strip or dipstick.

19. (Amended) The assay device or kit of claim 15 comprising as separate reagents antibodies to the apolipoprotein and antibodies to albumin.

20. (Twice amended) A method for quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease <u>from a saliva sample</u> comprising

[(a) reacting the apolipoproteins in a saliva sample with antibodies specifically immunoreactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, <u>and</u> Apo E[, and components thereof] in a quantitative assay,

(b) determining the amount of immunoreaction between the antibodies and the apolipoproteins in the saliva sample, and

(c) comparing the amount of immunoreaction determined in step b with the amount of immunoreaction of the antibodies immunoreactive with the apolipoprotein in the saliva sample]

<u>obtaining a saliva sample from an individual,</u>

<u>reacting the apolipoproteins in the saliva sample with antibodies immunoreactive with one or more of the apolipoproteins, wherein the antibodies are in a quantitative assay which</u>

measures the amount or concentration of bound complexes between apolipoproteins and the antibodies immunoreactive therewith,

determining the amount of apolipoproteins in the serum of the individual by comparing the immunoreactivity between the antibodies and apolipoproteins in the saliva sample by reference to standards of known amounts of apolipoproteins in saliva and serum from normal or at risk individuals.

21. (twice amended) The method of claim 1 further comprising,

correlating the levels of one or more lipoproteins selected from the group consisting of [HDL] high density lipoprotein [and/or] and [LDL] low density lipoprotein, in the serum with the levels of [apolipoproteins] apolipoprotein subtypes in the serum,

correlating the levels of the [apolipoproteins] apolipoprotein subtypes in the serum based on the levels of [apolipoproteins] apolipoprotein subtypes determined in the saliva sample, and

extrapolating the levels of [HDL and/or LDL] the lipoprotein in the serum, based on the levels of the [apolipoproteins] apolipoprotein subtypes determined in the saliva sample.

22. (amended) The method of claim 20 comprising reacting the apolipoprotein in the saliva sample with antibodies specifically immunoreactive with an apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, and Apo E, [and components thereof,] and

correlating the levels of at least one apolipoprotein in the saliva with the levels of apolipoprotein in serum samples of patients having [known to be correlated to the presence of] lipid disorders or risk of cardiovascular disease.